UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,345	01/14/2004	Sudhir Agrawal	HYB-018US1	3490

7590 11/10/2008

Joseph C. Zucchero
Keown & Associates
Suite 1200
500 West Cummings Park
Woburn, MA 01801

EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
11/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,345	AGRAWAL ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 3, 5, 10-16, 18, 31-32, 40, 42, 95, 99 and 147* is/are pending in the application.

4a) Of the above claim(s) *3,5,10-16,18,32,40,42,95,99 and 147* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action
Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 10, 2008 has been entered.

Election/Restrictions

Applicant has elected the invention of Group I, drawn to an immunomer compound comprising at least two oligonucleotides linked together, wherein Applicant has elected the oligonucleotide linkage species to be "iv", a sugar to a non-nucleotide linker and the "G" moiety species to be "2'-deoxy-7-deazaguanosine". However, upon further consideration, the Examiner has withdrawn the "G" species election requirement.

Election of Applicant's invention(s) was made without traverse.

Amendments

Applicant's response and amendments, filed October 3, 2008, to the prior Office Action is acknowledged. Applicant has cancelled Claims 2, 4, 6-9, 17, 19-30, 33-39, 41, 43-94, 96-98 and 100-146 and withdrawn Claims 3, 5, 10-16, 18, 32, 40 and 42.

The amendment filed October 3, 2008 is objected to for failing to comply with MPEP §1.121 Manner of making amendments in applications.

(c) Claims. Amendments to a claim must be made by rewriting the entire claim with all changes (e.g., additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers

in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).

> (1) Claim listing. All of the claims presented in a claim listing shall be presented in ascending numerical order. Consecutive claims having the same status of "canceled" or "not entered" may be aggregated into one statement (e.g., Claims 1-5 (canceled)). The claim listing shall commence on a separate sheet of the amendment document and the sheet(s) that contain the text of any part of the claims shall not contain any other part of the amendment.

In the instant case, the correct status of Claims 95, 99 and 147 is "withdrawn".

Claims 3, 5, 10-16, 18, 32, 40, 42, 95, 99 and 147 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1 and 31 are under consideration.

Priority

Applicant's claim for the benefit of a prior-filed parent provisional application 60/440,587 filed on January 16, 2003 under 35 U.S.C. 119(e) is acknowledged.

Accordingly, the effective priority date of the instant application is granted as January 16, 2003.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the October 10, 2008 response will be addressed to the extent that they apply to current rejection(s).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. **Claims 1 and 31 stand rejected under 35 U.S.C. 103(a)** as being unpatentable over Kandimalla et al (Bioorganic & Medicinal Chem. 9:807-813, 2001; *of record in IDS) in view of Kandimalla et al (WO 02/26757; *of record in IDS) and Simmonds et al (WO 99/06422, U.S. equivalent 6,444,682).

The claims are drawn to an immunomer compound comprising at least two oligonucleotides linked at their sugars to a non-nucleotidic linker, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide having the structure RpG, wherein the "R" moiety has the structure shown in Figure 24 and the "G" moiety is guanosine, 2'-deoxyguanosine, 2'-deoxy-7-deazaguanosine", 2'-deoxy-6-thioguanosine, arabinoguanosine, 2'-deoxy-2' substituted-arabinoguanosine, 2'O-substituted-arabinoguanosine, or other non-natural purine.

Determining the scope and contents of the prior art.

Kandimalla et al (2001) teach the synthesis of phosphorothioate CpG immunostimulatory oligonucleotides comprising variations of the CpG motif, YpG and CpR, respectively, in which the "Y" moiety represents a monocyclic or bicyclic cytosine analogue (pg 808, Figures 1 and 2) and the "R" moiety represents a bicyclic guanine analogue, including 2' deoxyguanosine, 2'-deoxy-7-deazaguanosine, and other non-natural purine nucleosides (pg 809, Figure 3).

Kandimalla et al (2001) do not teach the "C" or "Y" moiety to represent a bicyclic cytosine analogue in combination with a plurality of possible "G*" groups in the context of two oligonucleotides linked together by one of a plurality of linkages. However, at the time of the invention, Kandimalla et al ('757) disclosed a genus of CpG immunostimulatory oligonucleotides, wherein positional modification of immunostimulatory oligonucleotides dramatically affects their immunostimulatory capabilities. In particular, modifications in the immunostimulatory domain and/or the potentiation domain enhance the immunostimulatory effect in a reproducible and predictable manner (pg 5, lines 7-11). Kandimalla et al disclose immunostimulatory oligonucleotides coupled to each other via a 3'-3' linkage or internucleoside linkages or a functionalized nucleobase or sugar to a non-nucleotidic linkers (pg 10, line 24- pg 11, lines 1-20; pg 14, lines 18-29), wherein the immunostimulatory domain comprises a dinucleotide analogue that includes a non-natural pyrimidine nucleoside, a modified nucleoside, deazanucleosides, or any combination thereof (pg 10, lines 22-27), wherein the sugar may be a 2'-deoxyribose (pg 13, line 13), the C*pG* motif comprises a C* that may be a non-natural purine (pg 13, line 22) and a G* that may be 2'-deoxy-7-deazaguanosine, 2'-deoxy-6-thioguanosine, 2'-substituted arabinose sugars, other non-natural purine nucleosides (pg 13, lines

11-15; pg 14, lines 10-17; pg 15, lines 6-10; pg 23, lines 10-11). Kandimalla et al disclose that cytosine has two hydrogen bond acceptor groups at positions 2 (keto-oxygen) and 3 (nitrogen), and a hydrogen bond donor group at the 4-position (amino group). These groups can serve as potential recognizing and interacting groups wit receptors that are responsible for immune stimulation, wherein one embodiment of a cytosine analogue is the bicyclic, non-natural purine illustrated in Figure 28, Compound #7, "deoxy-P-base" (pg 12, lines 11-20).

Neither Kandimalla et al (2001) nor Kandimalla et al ('757) teach the C* motif may be the bicyclic cytosine analogue 2-oxo-7-deaza-8-methylpurine that possesses the "R" structure shown in Figure 24. However, at the time of the invention, Simmonds et al disclosed novel nucleoside or base analogues having the structure illustrated in Figure 24 of the instant specification (Abstract, pgs 1-2), wherein such novel base analogues may be incorporated into nucleic acids and oligonucleotides (pg 1, lines 5-7; pg 6, lines 1-2).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in functional equivalents and analogues of nucleic acids and chemical synthesis of immunostimulatory oligonucleotides. Therefore, the level of ordinary skill in this art is high.

All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination(s) would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to try substituting a bicyclic non-natural cytosine analogue as taught by Kandimalla et al (2001, '757) with a bicyclic non-natural cytosine analogue having the structure shown in Figure 24 (Simmonds et al) with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention, and "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common sense." Kandimalla et al ('757) disclose that a bicyclic cytosine analogue may be used together with a guanosine analogue, i.e. 2'-deoxy-7-deazaguanosine, to yield an immunostimulatory oligonucleotide.

An artisan would be motivated to try substituting a bicyclic non-natural cytosine analogue as taught by Kandimalla et al ('757) with a bicyclic non-natural cytosine analogue having the structure shown in Figure 24 as taught by Simmonds et al because both the bicyclic P-base analogueue (Kandimalla et al ('757); Figure 28, compound #7) and the bicyclic cytosine analogue 2-oxo-7-deaza-8-methylpurine (Simmonds) share the oxygen and nitrogen hydrogen

bond acceptor atoms and nitrogen hydrogen bond donor atom on the same face so as to establish hydrogen bonding with another surface in the same manner as cytosine, and Kandimalla et al teach that positional modification of immunostimulatory oligonucleotides dramatically affects their immunostimulatory capabilities in a reproducible and predictable manner (pg 5, lines 7-11), thereby motivating the artisan to improve and optimize the design of an immunostimulatory oligonucleotide having the desired immunostimulatory effect.

Thus, the invention as a whole is *prima facie* obvious.

Response to Arguments

Applicant argues that Kandimalla ('757) does not disclose "two oligonucleotides linked at their 3' ends via a non-nucleotidic linker".

Applicant's argument(s) has been fully considered, but is not persuasive. The nature of such confusion and/or Applicant's interpretation is unclear to the Examiner because Kandimalla et al disclose immunostimulatory oligonucleotides coupled to each other via a 3'-3' linkage or internucleoside linkages or a functionalized nucleobase or sugar to a non-nucleotidic linkers (pg 10, line 24- pg 11, lines 1-20; pg 14, lines 18-29; see also claims 20 and 29).

Response to Amendment

The Kandimalla Declaration under 37 CFR 1.132 filed October 3, 2008 is insufficient to overcome the rejection of claims 1 and 31 based upon Kandimalla et al (2001) in view of Kandimalla et al (WO 02/26757) and Simmonds et al (WO 99/06422, U.S. equivalent 6,444,682) as set forth in the last Office action.

Applicant argues that some of the modifications reduced or abolished the immunostimulatory activity of the oligonucleotide, while others increased the immunostimulatory activity. One modification referred to in the present rejection is the substitution of the unmethylated-C in the CG dinucleotide with the bicyclic cytosine analogue deoxy-P-base. As stated in Kandimalla (2001), modifying the CG dinucleotide with deoxy-P-base resulted in an oligonucleotide that showed little or no immunostimulatory activity. As an author of this reference, I can attest that this meant that it was a non-functioning molecule and that the phrase "showed little or no immunostimulatory activity" meant that those modifications were inactive (i.e., not immunostimulatory). Therefore, contrary to the assertion in the Office Action, this oligonucleotide does not meet the functional limitations of the instantly claimed genus. (¶5) Despite any structural similarity between deoxy-P-base and the instantly claimed

modification, a CG-containing oligonucleotide having a deoxy-P-base modification resulted in a non-functioning molecule whereas the instantly claimed modification resulted in a functional molecule. (¶6)

Applicant's argument(s) has been fully considered, but is not persuasive.

As a first matter, Kandimalla et al (2001) teach the simple substitution of an unmethylated cytosine for cytosine analogues that are isostructural with natural cytosine, including a P-base, thereby demonstrating that substituting cytosine for a P-base in an oligonucleotide that is to be assayed for immunstimulatory activity is routine.

As a second matter, while Kandimalla et al (2001) teach only one species of a P-base cytosine analogue, those of ordinary skill in the art (Simmonds et al) recognize the existence of a genus of P-base cytosine analogues, including the instantly claimed analogue illustrated in Figure 24 of the instant application. It is well within the skills of the ordinary artisan to substitute a first P-base cytosine analogue for a second P-base cytosine analogue.

As a third matter, Applicant's own work (Kandimalla et al, 2001) clearly demonstrates that while not all cytosine analogue species may be functional as per the artisan's desired degree of efficacy, several species within a given genus need to be tested/assayed for activity to draw a real-world, scientifically meaningful conclusion. For example, only two of the five monocyclic cytosine analogues, analogues 4 and 6 (Figure 2), demonstrated immunostimulatory activity. Thus, the result yielded by the analogue 7 P-base does not clearly and absolutely teach away from all other species within the genus of P-base cytosine analogues (Applicant's argument) because Applicant clearly teaches that other species of similar structure should be tested as there are other isostructural cytosine analogue species from which the ordinary artisan may reasonably expect (at least 40% probability of success, as per 2/5 of the monocyclic cytosine analogues) to detect immunostimulatory activity when assayed under the appropriate conditions. Thus, at the time of the invention, those of ordinary skill in the art had both taught, suggested and possessed a reasonable expectation of success that a P-base would function as a cytosine substitute (C*) in an immunostimulatory oligonucleotide comprising a C*pG motif.

The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure:

Krieg et al (U.S. 2004/0053880 A1) disclosed immunostimulatory nucleic acids comprising CpG motifs, wherein the cytosine may be substituted with a P-base [0094].

Fearon et al (U.S. Patent 7,255,868) disclosed immunostimulatory nucleic acids comprising CpG motifs, wherein the cytosine may be substituted with an isostructural bicyclic analog (col. 30, line 45-col. 31, line 40).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. **Claims 1 and 31 are rejected** on the ground of nonstatutory obviousness-type double patenting over Claims 37, 39, 40 and 52-59 of copending Application No. 10/279,684 (now U.S. Patent 7,276,489) in view of Simmonds et al (WO 99/06422, U.S. equivalent 6,444,682).

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunomers having at least two oligonucleotides linked together by a non-nucleotidic linker, wherein the internucleoside linkage is a phosphorothioate, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5' end and

comprising an immunostimulatory dinucleotide having the structure RpG, wherein the "R" a non-natural pyrimidine nucleoside and wherein the "G" moiety is guanosine, 2'-deoxyguanosine, 2'-deoxy-7-deazaguanosine", 2'-deoxy-6-thioguanosine, arabinoguanosine, 2'-deoxy-2' substituted-arabinoguanosine, 2'O-substituted-arabinoguanosine, or other non-natural purine. Because the instant claim uses the generic term "internucleoside linkage", the Examiner has looked to the specification for a definition to better understand the invention, wherein a genus of internucleotide linkages are disclosed (pg 7, lines 5-8) substantially as claimed in the co-pending application, and wherein the immunomer may be conjugated to an antigen (pg 7, lines 16-20).

'489 does not disclose the synthetic purine illustrated in Figure 24 of the instant application. However, at the time of the invention, Simmonds et al disclosed novel nucleoside or base analogues having the structure illustrated in Figure 24 of the instant specification (Abstract, pgs 1-2), wherein such novel base analogues may be incorporated into nucleic acids and oligonucleotides (pg 1, lines 5-7; pg 6, lines 1-2).

An artisan would be motivated to try substituting a non-natural cytosine analogue with a bicyclic non-natural cytosine analogue having the structure shown in Figure 24 as taught by Simmonds et al because at the time of the invention, those of ordinary skill in the art were aware of cytosine isostructural analogues such as that disclosed in Figure 24 of the instant application share the oxygen and nitrogen hydrogen bond acceptor atoms and nitrogen hydrogen bond donor atom on the same face so as to establish hydrogen bonding with another surface in the same manner as cytosine, and Agrawal et al teach that positional modification of immunostimulatory oligonucleotides dramatically affects their immunostimulatory capabilities in a reproducible and predictable manner, thereby motivating the artisan to improve and optimize the design of an immunostimulatory oligonucleotide having the desired immunostimulatory effect.

Thus, instantly claimed immunomer composition(s) are obvious variants of the immunomers of '383 because at the time of the invention, those of ordinary skill in the art were aware of cytosine isostructural analogues such as that disclosed in Figure 24 of the instant application, wherein cytosine isostructural analogues may be used in combination with guanosine or guanosine analogues in the synthesis of immunomer compounds comprising at least two oligonucleotides linked at their 3' ends substantially as claimed.

3. **Claims 1 and 31 are provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claim 12 of copending Application No. 10/694,383 (U.S. 2004/0266710) in view of Simmonds et al (WO 99/06422, U.S. equivalent 6,444,682).

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunostimulatory oligonucleotide compositions comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a non-natural purine nucleoside.

The claims are drawn to an immunostimulatory oligonucleotide compound comprising a "YpZ" motif, wherein the "Y" moiety is a non-natural pyrimidine and the "Z" moiety is guanosine, 2'-deoxy-guanosine or a non-natural purine nucleoside. Because the claim uses the generic term "compound", the Examiner has looked to the specification for a description of the invention, wherein the specification discloses that the immunostimulatory oligonucleotides may be joined by 3' to 3' linkages (pg 10, line 23-pg 12, line 9). The "Y" moiety of '383 may be a non-natural pyrimidine nucleoside, such as a P-base (Figure 28), wherein the "R" non-natural purine shown in Figure 24 and claimed in the instant application is a heterocyclic compound having the structure of a non-natural pyrimidine. Thus, the "non-natural pyrimidine" ('383) is also a "synthetic purine" (instant application).

'383 does not disclose the synthetic purine illustrated in Figure 24 of the instant application. However, at the time of the invention, Simmonds et al disclosed novel nucleoside or base analogues having the structure illustrated in Figure 24 of the instant specification (Abstract, pgs 1-2), wherein such novel base analogues may be incorporated into nucleic acids and oligonucleotides (pg 1, lines 5-7; pg 6, lines 1-2).

An artisan would be motivated to try substituting a bicyclic non-natural cytosine analogue as taught by Kandimalla et al ('383) with a bicyclic non-natural cytosine analogue having the structure shown in Figure 24 as taught by Simmonds et al because both the bicyclic P-base analogueue (Kandimalla et al ('383); Figure 28, compound #7) and the bicyclic cytosine analogue 2-oxo-7-deaza-8-methylpurine (Simmonds) share the oxygen and nitrogen hydrogen bond acceptor atoms and nitrogen hydrogen bond donor atom on the same face so as to establish hydrogen bonding with another surface in the same manner as cytosine, and Kandimalla et al teach that positional modification of immunostimulatory oligonucleotides dramatically affects

their immunostimulatory capabilities in a reproducible and predictable manner, thereby motivating the artisan to improve and optimize the design of an immunostimulatory oligonucleotide having the desired immunostimulatory effect.

Thus, instantly claimed immunomer composition(s) are obvious variants of the immunomers of '383 because at the time of the invention, those of ordinary skill in the art were aware of cytosine isostructural analogues such as that disclosed in Figure 24 of the instant application, wherein cytosine isostructural analogues may be used in combination with guanosine or guanosine analogues in the synthesis of immunomer compounds comprising at least two oligonucleotides linked at their 3' ends substantially as claimed.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

4. **Claims 1 and 31 are provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claims 20-21 of copending Application No. 10/694,586 (U.S. 2006/0142224) in view of Simmonds et al (WO 99/06422, U.S. equivalent 6,444,682).

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunostimulatory oligonucleotide compositions comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a non-natural purine nucleoside.

The claims are drawn to an immunostimulatory oligonucleotide compound comprising a "CpG" motif, wherein the "C" moiety is a non-natural pyrimidine and the "G" moiety is a natural or non-natural pyrimidine nucleoside. Because the claim uses the generic term "compound", the Examiner has looked to the specification for a description of the invention, wherein the specification discloses that the immunostimulatory oligonucleotides may be joined by 3' to 3' linkages (pg 5, lines 18-20; Figure 17). Thus, instantly claimed immunomer composition(s) are reasonably embraced by immunostimulatory oligonucleotide(s) of the copending application. The "Y" moiety of '586 may be a non-natural pyrimidine nucleoside, such as a P-base (Figure 28), wherein the "R" non-natural purine shown in Figure 24 and claimed in the instant application is a heterocyclic compound having the structure of a non-

natural pyrimidine. Thus, the "non-natural pyrimidine" ('586) is also a "synthetic purine" (instant application).

'586 does not disclose the synthetic purine illustrated in Figure 24 of the instant application. However, at the time of the invention, Simmonds et al disclosed novel nucleoside or base analogues having the structure illustrated in Figure 24 of the instant specification (Abstract, pgs 1-2), wherein such novel base analogues may be incorporated into nucleic acids and oligonucleotides (pg 1, lines 5-7; pg 6, lines 1-2).

An artisan would be motivated to try substituting a bicyclic non-natural cytosine analogue as taught by Kandimalla et al ('586) with a bicyclic non-natural cytosine analogue having the structure shown in Figure 24 as taught by Simmonds et al because both the bicyclic P-base analogueue (Kandimalla et al ('586); Figure 28, compound #7) and the bicyclic cytosine analogue 2-oxo-7-deaza-8-methylpurine (Simmonds) share the oxygen and nitrogen hydrogen bond acceptor atoms and nitrogen hydrogen bond donor atom on the same face so as to establish hydrogen bonding with another surface in the same manner as cytosine, and Kandimalla et al teach that positional modification of immunostimulatory oligonucleotides dramatically affects their immunostimulatory capabilities in a reproducible and predictable manner, thereby motivating the artisan to improve and optimize the design of an immunostimulatory oligonucleotide having the desired immunostimulatory effect.

Thus, instantly claimed immunomer composition(s) are obvious variants of the immunomers of '586 because at the time of the invention, those of ordinary skill in the art were aware of cytosine isostructural analogues such as that disclosed in Figure 24 of the instant application, wherein cytosine isostructural analogues may be used in combination with guanosine or guanosine analogues in the synthesis of immunomer compounds comprising at least two oligonucleotides linked at their 3' ends substantially as claimed.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

5. **Claim 1 stands provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claim 1 of copending Application No. 10/361,111 (U.S. 2004/0156825).

Note: A Notice of Allowance of Claim 1 of 10/361,111 was mailed December 21, 2007.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunomers having at least two oligonucleotides linked

together by a non-nucleotidic linker, wherein the internucleoside linkage is modified, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a non-natural purine nucleoside. Thus, although the subject matter is recited using different terms, the composition(s) of the instant claim(s) is reasonably embraces and anticipates the composition(s) recited in the copending application.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

6. **Claims 1 and 31 stand provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claim 18 of copending Application No. 10/865,245.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunostimulatory oligonucleotide compositions comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a non-natural purine nucleoside.

The claims are drawn to an immunostimulatory oligonucleotide compound comprising a "CpG" motif, wherein the "C" moiety is a non-natural pyrimidine and the "G" moiety is a natural or non-natural pyrimidine nucleoside, wherein the immunostimulatory oligonucleotides may be joined by 3' to 3' linkages. Thus, instantly claimed immunomer composition(s) are reasonably embraced by immunostimulatory oligonucleotide(s) of the copending application. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

7. **Claims 1 and 31 stand provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claims 1-5, 16, 21-23 of copending Application No. 10/925,873.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunostimulatory oligonucleotide compositions comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a non-natural purine nucleoside.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunomers having at least two oligonucleotides linked together by a non-nucleotidic linker, wherein the internucleoside linkage is a phosphorothioate, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide having the structure C*pG*, wherein the "C*" a non-natural pyrimidine nucleoside and wherein the "G*" moiety is guanosine, 2'-deoxyguanosine, 2'-deoxy-7-deazaguanosine", 2'-deoxy-6-thioguanosine, arabinoguanosine, 2'-deoxy-2' substituted-arabinoguanosine, 2'O-substituted-arabinoguanosine, or other non-natural purine. Because the instant claim uses the generic term "internucleoside linkage", the Examiner has looked to the specification for a definition to better understand the invention, wherein a genus of internucleotide linkages are disclosed (pg 7, lines 5-8) substantially as claimed in the co-pending application, and wherein the immunomer may be conjugated to an antigen (pg 7, lines 16-20). Thus, the composition(s) of the instant claim(s) is reasonably embraced by the copending application.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

8. **Claims 1 and 31 stand provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claims 11-13 and 16 of copending Application No. 11/153,054.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunostimulatory oligonucleotide compositions comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a non-natural purine nucleoside.

Because the claims of copending Application No. 11/153,054 recite generically "CpG, C*pG, C*pG* and CpG*", the Examiner has looked to the specification for definitions of the "C" and "G" moieties so as to better understand the invention. The specification discloses that C* is… 1-(2'-deoxy-β-D-ribofuranosyl)-2-oxo-7-deaza-8-methyl-purine, and that G* is… 2'-deoxy-7-deazaguanosine (pg 1, [0010]), wherein the non-nucleotidic linker may be a 3'-3' linkage (pg 3, [0032]). Thus, instantly claimed immunomer composition(s) anticipate immunostimulatory oligonucleotide(s) of the copending application.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

9. **Claims 1 and 31 stand provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claims 1 and 4 of copending Application No. 11/174,002 (U.S. 2006/0211641).

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunostimulatory oligonucleotide compositions comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a natural or non-natural purine nucleoside.

Thus, instantly claimed immunomer composition(s) anticipate immunostimulatory oligonucleotide(s) of the copending application.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Response to Arguments

Applicant argues that Applicants will consider filing a Terminal Disclaimer or take any other action deemed necessary in the later filed, copending applications 10/361,111, 10/865,245, 10/925,873, 11/153,054 and 11/174,002.

Applicant's argument(s) has been fully considered, but is not persuasive. Applicant has not filed a Terminal Disclaimer or taken any other action deemed necessary in the later filed, copending applications as it pertains to the instant application. The provisional nonstatutory

obviousness-type double patenting rejections will be maintained until all claims have been deemed otherwise in condition for allowance or allowable.

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Examiner, Art Unit 1633

/Q. JANICE LI, M.D./
Primary Examiner, Art Unit 1633